IMMUNE REGULATION

Leading role for *FOXP3*

The programmed differentiation of $CD4^+$ T helper (T_H) cells into distinct effector lineages seems to be controlled by two key genes, *T-bet* and *GATA3*, which encode transcription factors that are essential for T_H1- and T_H2-cell development, respectively. Now, researchers have identified what might be the equivalent master gene for the development of $CD4^+$ regulatory T (T_{Reg}) cells.

Recently, the human disease IPEX (immune dysregulation, polyendocrinopathy and entereropathy, X-linked) and its mouse counterpart, the Scurfy mutant, were found to be caused by mutations in the *FOXP3* (forkhead box P3) gene, which encodes a forkhead/winged-helix transcription factor. Shimon Sakaguchi and his team were struck by the similarities between IPEX syndrome and the multi-organ autoimmunity that occurs in mice that are deficient for the naturally occurring $CD4^+CD25^+$ population of T_{Reg} cells, and they wondered if FOXP3 is involved in the development of these cells.

In support of this hypothesis, they found that *Foxp3* is expressed predominantly by $CD4^+CD25^+$ T cells. Next, they tested whether forced expression of *Foxp3* could turn a naive T cell into a T_{Reg} cell. Peripheral $CD4^+CD25^-$ T cells from normal mice were induced to express *Foxp3* by retroviral transduction. Similar to prototypical T_{Reg} cells, the *Foxp3*-expressing cells proliferated poorly and secreted little interleukin-2 (IL-2), interferon-γ, IL-4 or IL-10 in response to T-cell receptor stimulation. Moreover, the *Foxp3*-transduced T cells expressed higher levels of T_{Reg}-cell-associated molecules, such as CD25, CTLA4, GITR and CD103, than the non-transduced cells.

But, can the *Foxp3*-transduced T cells actually regulate immune responses? *In vitro*, these cells inhibited the proliferation of non-transduced T cells and, similar to naturally occurring $CD25^+CD4^+$ T_{Reg} cells, this suppression required cell–cell contact.

However, the true test of a T_{Reg} cell is whether it can suppress autoimmune and inflammatory diseases *in vivo*. If lymphocyte-deficient mice are reconstituted with $CD4^+CD25^-$ T cells only, they develop severe autoimmune gastritis and inflammatory bowel disease, which can be prevented by the co-transfer of naturally occurring $CD4^+CD25^+$ T_{Reg} cells. Similarly, *Foxp3*-transduced T cells were found to prevent disease, which indicates that expression of *Foxp3* can convert a naive T cell into a fully fledged regulator.

This study supports the idea that *FOXP3* is an essential instructor of $CD4^+CD25^+$ T_{Reg}-cell development, which is of importance both practically, as FOXP3 could be the first specific marker of T_{Reg} cells, and clinically, as it provides a potential target for the therapeutic manipulation of $CD4^+CD25^+$ T_{Reg} cells.

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References and links

ORIGINAL RESEARCH PAPER Hori, S., Nomura, T. & Sakaguchi, S. Control of regulatory T-cell development by the transcription factor FOXP3. *Science* 9 January 2003 (DOI: 10.1126/science.1079490)

IN BRIEF

INFLAMMATION

Essential role for proteinase-activated receptor-2 in arthritis.

Ferrell, W. R. *et al. J. Clin. Invest.* **111**, 35–41 (2003)

The G-protein-coupled receptor proteinase-activated receptor 2 (PAR2) has been implicated previously as a mediator of acute inflammation. Here, Ferrell *et al.* used an adjuvant monoarthritis model to investigate the role of PAR2 in chronic inflammation. *Par2*$^{-/-}$ mice were generated and used in these studies. The severity of chronic arthritis was reduced by a factor of more than four in the *Par2*$^{-/-}$ mice compared with wild-type mice. In addition, PAR2 agonists had potent pro-inflammatory effects, resulting in prolonged joint swelling and vasodilation. So, PAR2 has an essential role in mediating chronic inflammation, and it might be an important therapeutic target for the management of chronic inflammatory diseases.

THYMOCYTE DEVELOPMENT

Thymopoiesis independent of common lymphoid progenitors.

Allman, D. *et al. Nature Immunol.* 6 January 2003 (DOI: 10.1038/ni878)

Thymocytes develop from blood-borne haematopoietic progenitors that seed the thymus, but the source of these early thymic progenitors (ETPs) is unknown. Common lymphoid progenitors (CLPs) in adult bone marrow, which can develop into B or T cells, were seen as a likely suspect. However, as this study shows, ETPs and CLPs differ with respect to their responsiveness to interleukin-7 and the kinetics with which they generate B and T cells. Also, *Ikaros*$^{-/-}$ mice, which have normal T-cell development, but are blocked for B-cell development, have normal levels of ETPs although CLPs are undetectable. Therefore, the authors conclude that ETPs develop from an early progenitor population that is distinct from CLPs.

MYELOID DEVELOPMENT

Intrinsic requirement for zinc finger transcription factor Gfi-1 in neutrophil differentiation

Hock, H. *et al. Immunity* **18**, 109–120 (2003)

Previous studies have shown that the transcription factors PU.1, C/EBPα and C/EBPε are essential for neutrophil differentiation. Here, Hock *et al.* show that the nuclear zinc-finger transcriptional repressor Gfi1 is also intrinsically required for neutrophil development. *Gfi1*$^{-/-}$ mice survive to ~11 weeks of age, and they are highly susceptible to abscess formation by Gram-positive bacteria. Mature neutrophils were shown to be absent from the blood of these gene-targeted mice, and immature neutrophils were lacking in the bone marrow. Instead, morphologically arrested, atypical $Gr1^+Mac1^+$ myeloid cells with characteristics of both neutrophils and macrophages (respiratory burst and phagocytosis) were present. Re-expression of *Gfi1* in *Gfi1*$^{-/-}$ granulocyte/monocyte progenitors rescued normal neutrophil differentiation and blocked development of the atypical myeloid cells.